

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: **Tibor Sipos et al.**

Prior Application Serial No.: 10/100,716

Prior Filing Date: March 19, 2002

For: **COMPOSITION AND METHOD TO
PREVENT OR REDUCE DIARRHEA AND
STEATORRHEA IN HIV-POSITIVE
PATIENTS**

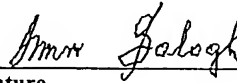
CERTIFICATE UNDER 37 C.F.R. 1.10

Express Mail Label Number: ER 382 395040 US

Date of Deposit: _____

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service on the date indicated above and is addressed to: Mail Stop Patent Application, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Signature



Mail Stop Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with the suggested procedure of 37 CFR 1.97 and 1.98, Applicants are submitting herewith copies of all of the prior art references identified on the enclosed list, which are considered to comprise the closest prior art of which the undersigned attorney, the inventors and anyone else believed to have been substantially involved in the preparation of this application are aware. Each of the patent references will be discussed below in a brief paragraph.

1. U.S. Patent No. 5,578,304, issued to Tibor Sipos on November 26, 1996, discloses gastric acid-resistant polymer-coated, buffered digestive enzymes/ursodeoxycholate compositions for the treatment of digestive disorders, pancreatic enzyme insufficiency, impaired liver function and cystic fibrosis. The compositions comprise from 10% to 90% w/w of an enzyme selected from the group consisting of pancreatic proteases, pancreatic lipases, pancreatic nucleases and pancreatic amylases.

There is no suggestion in the patent to use the compositions in HIV-positive patients who are treated with High Activity Antiretroviral drugs for reducing/eliminating diarrhea or steatorrhea.

2. U.S. Patent No. 5,460,812, issued to T. Sipos on October 24, 1995, discloses a buffered digestive enzyme/bile salt compositions for the treatment of digestive enzyme/bile salt deficiency comprising: 10% to 90% w/w of an enzyme selected form the group consisting of: pancreatin, pancreatic proteases, pancreatic lipases, pancreatic nucleases and pancreatic amylases; 0.3 to 75% w/w of a bile sat; and 5 to 40% w/w of a buffering agent.

There is no suggestion in the patent to use the compositions in HIV-positive patients who are treated with High Activity Antiretroviral drugs for reducing/eliminating diarrhea or steatorrhea.

3. U.S. Patent No. 5,324,514, issued to Tibor Sipos on June 28, 1994, discloses a digestive enzyme/bile salt composition for the treatment of digestive enzyme/bile salt deficiency comprising:

- about 71 to 90% w/w of an enzyme selected from the group consisting of pancreatic proteases, lipases, nucleases, and amylases;
- about 0.3 to 13% w/w of a bile salt; and
- about 0.8% to about 5% w/w of a buffering agent.

There is no suggestion in the patent to use the compositions in HIV-positive patients who are treated with High Activity Antiretroviral drugs for reducing/eliminating diarrhea or steatorrhea.

4. U.S. Patent No. 5,260,074, issued to Tibor Sipos on November 9, 1993, discloses gastric acid-resistant polymer-coated digestive enzymes/ursodeoxycholate compositions for treating digestive disorders, impaired liver function, and cystic fibrosis. The composition comprises:

- of from about 71 to about 90% w/w of an enzyme selected from the group consisting of pancreatic proteases, lipases, nucleases and amylases;

about 1.0 to about 61% w/w of a salt of ursodeoxycholic acid selected from the group consisting of sodium, potassium, ammonium, tromethamine, ethanolamine, diethanolamine, and triethanolamine; and

about 0.8 to about 5.0% w/w of a buffering agent consisting of: sodium, potassium, ammonium, tromethamine, ethanolamine, diethanolamine and triethanolamine.

There is no suggestion in the patent to use the compositions in HIV-positive patients who are treated with High Activity Antiretroviral drugs for reducing/eliminating diarrhea or steatorrhea.

5. U.S. Patent No. 4,079,125, issued to Tibor Sipos on March 14, 1978, discloses an enteric-coated digestive enzyme-containing composition comprising:

an enzyme selected from the group consisting of pancreatic proteases, lipases, nucleases and amylases;

a binder system consisting of polyvinylpyrrolidone, microcrystalline cellulose, cellulose acetate phthalate, methylcellulose and alginic acid;

a stabilizer selected from the group consisting of calcium carbonate, polyvinylpyrrolidone, cellulose acetate phthalate, methyl cellulose, starch and alginic acid;

a disintegrant selected from the group consisting of citric acid, sodium carbonate, sodium bicarbonate, calcium carbonate, microcrystalline cellulose and alginic acid; and

a coating of a non-porous, enteric coating which is insoluble in the pH range of 1.5 to 5 but is soluble in the pH range of 6 to 9.

The enzyme is selected from the group consisting of Trypsin, Chymotrypsine, Chymotrypsin B, Glycerol Ester Hydrolase, Phospholipase A₂, Sterol ester hydrolase, Ribonuclease, Deoxyribonuclease, α -Amylase, Papain, Chymopapain, Bromelain, Ficin, β -Amylase, Cellulase, β -Galactosidase, Subtilopeptidase and Aspergillopeptidase A.

There is no suggestion in the patent to use the compositions in HIV-positive patients who are treated with High Activity Antiretroviral drugs for reducing/eliminating diarrhea or steatorrhea.

6. U.S. Patent No. 4,280,971, issued to Wischniewski et al. on July 28, 1981, discloses pancreatic pellets comprising at least 80% w/w of pancreatin.

There is no suggestion in the patent to use the compositions in HIV-positive patients who are treated with High Activity Antiretroviral drugs for reducing/eliminating diarrhea or steatorrhea.

7. U.S. Patent No. 5,378,462, issued to Boedecker et al. on January 3, 1995, discloses pancreatin micropellets comprising:

65 to 85% w/w of pancreatin;
15 to 50% w/w of polyethylene glycol 4000; and
a gastric juice-resistant film which coats the micropellets.

8. *Am. J. Gastroenterol* (2001) 96:1831-1837; Last update: 7/18/2001 14:34:20 EDT Reuters Health by Anthony J. Brown, M.D.: "Fat malabsorption common cause of diarrhea in HIV-infected patients".

9. *Clinical Infectious Diseases*, (2000) 30:408-414, Sherman et al. "Management of Protease Inhibitor-Associated Diarrhea".

10. *Merck Index* (2001) 13th Edition; All antiviral.

Amprenavir	Stavudine
Ritonavir	Abacavir
Nelfinavir	Delavirdine
Saquinavir	Efavirenz
Indinavir	Zaigen
Lambivudine	Delavardine Mesylate
Zidovudine	Sustiva
Zalcitabine	Viromune
Didanosine	Nevirapine

11. U.S. Patent No. 6,313,296, issued to Sham et al. on November 6, 2001, discloses HIV protease inhibitor compounds.
12. U.S. Patent No. 6,303,786, issued to Deason et al. on October 16, 2001, discloses HIV protease inhibitors.
13. U.S. Patent No. 6,284,767, issued to Sham et al. on September 4, 2001, discloses retroviral protease inhibiting compounds.
14. U.S. Patent No. 6,257,906, issued to Chen et al. on June 26, 2001 discloses retroviral protease inhibiting compounds.
15. U.S. Patent No. 6,184,241, issued to P. Baures on February 6, 2001, discloses retroviral protease inhibiting compounds.
16. U.S. Patent No. 6,180,634, issued to Vacca et al. on January 30, 2001, discloses a combination therapy for the treatment of AIDS.
17. U.S. Patent No. 6,147,095, issued to Ferry et al. on November 14, 2000, discloses a method for improving the pharmacokinetics of tipranovir.
18. U.S. Patent No. 6,117,999, issued to Babu et al. on September 12, 2000, discloses methods of making HIV-protease inhibitors and intermediates for making HIV-protease inhibitors.
19. U.S. Patent No. 6,170,277, issued to Tucker et al. on August 8, 2000, discloses retroviral protease inhibiting combinations.
20. U.S. Patent No. 6,005,103, issued to Domagala et al. on December 21, 1999, discloses pyrone derivatives as protease inhibitors and antiviral agents.
21. U.S. Patent No. 5,981,759, issued to Sun et al. on November 9, 1999, discloses a process for indinavir intermediates.

22. U.S. Patent No. 5,977,086, issued to Lisiewicz et al. on November 2, 1999, discloses a method of inhibiting human immunodeficiency virus by combined use of hydroxyurea, a nucleoside analog, and a protease inhibitor.
23. U.S. Patent No. 5,962,725, issued to Deason et al. on October 5, 1999, discloses intermediate compounds useful for making HIV protease inhibitors such as nelfinavir.
24. U.S. Patent No. 5,945,413, issued to Tung et al. on August 31, 1999, discloses aspartyl protease inhibitors.
25. U.S. Patent No. 5,905,068, issued to Chen et al. on May 18, 1999, discloses retroviral protease inhibiting compounds.
26. U.S. Patent No. 5,837,729, issued to A. Bourinbaier on November 17, 1998, discloses methods for treating and preventing HIV infection using acetaminophan and derivatives thereof.
27. U.S. Patent No. 5,804,552, issued to Basava et al. on September 8, 1998, discloses lipid conjugates of therapeutic peptides and protease inhibitors.
28. U.S. Patent No. 5,760,076, issued to Vazquez et al. on June 2, 1998, discloses succinoylamino hydroxyethylamino sulfonamides useful as retroviral protease inhibitors.
29. U.S. Patent No. 5,756,319, issued to Furuta et al., on May 26, 1998, discloses a process for making S-phenyl-L-cystine.
30. U.S. Patent No. 5,750,493, issued to Sommadossi et al. on May 12, 1998, discloses a method to improve the biological and antiviral activity of protease inhibitors.

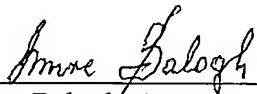
31. U.S. Patent No. 5,725,873, issued to Cook et al. on March 10, 1998, discloses a method of improving the growth or the efficiency of feed conversions of an animal and compositions for use therein.

32. U.S. Patent No. 5,616,578, issued to M. Otto on April 1, 1997, discloses a method of treating human immunodeficiency virus infection using a cyclic protease inhibitors in combination with a reverse transcriptase inhibitor.

There is no suggestion in the above-cited references to use a composition or method for treating/reducing diarrhea or steatorrhea in HIV-positive patients.

Respectfully submitted,

Date: April 8, 2004



Imre Balogh, Attorney for Applicant
Registration No. 26,835

Address:
276 Smith School Road
Perkasie, PA 18944
Phone (215) 249-9287
Facsimile (215) 249-1286

Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	ATTY. DOCKET NO. TS-008(CIP)	SERIAL NO.
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use several sheets if necessary)</i>		APPLICANT Tibor Sipos et al.	
		FILING DATE	GROUP

U.S. PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
	6,100,277 ✓	08/08/00	Tucker et al.			
	6,005,103 ✓	12/21/99	Domagala et al.			
	5,981,759 ✓	11/09/99	Sun et al.			
	5,977,086 ✓	11/02/99	Lisiewicz et al.			
	5,962,725 ✓	10/05/99	Deason et al.			
	5,945,413 ✓	08/31/99	Tung et al.			
	5,905,068 ✓	05/18/99	Chen et al.			
	5,837,729 ✓	11/17/98	Bourinbair			
	5,804,552 ✓	09/08/98	Basaya et al.			
	5,760,076 ✓	07/02/98	Vazquez et al.			
	5,756,319 ✓	05/26/98	Vazquez et al.			
	5,750,493 ✓	05/12/98	Sommadossi et al.			
	5,725,873 ✓	03/10/98	Al-Razzak et al.			
	5,616,578 ✓	04/01/97	Otto			

FOREIGN PATENT DOCUMENTS

	Document Number	Date	Country	Class	Subclass	Translation	
						Yes	No

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER	DATE CONSIDERED	
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.		

Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	ATTY. DOCKET NO. TS-008(CIP)	SERIAL NO.
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use several sheets if necessary)</i>		APPLICANT Tibor Sipos et al.	
		FILING DATE	GROUP

U.S. PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
	5,578,304 ✓	11/26/96	Tibor Sipos			
	5,460,812 ✓	10/24/95	Tibor Sipos			
	5,324,514 ✓	06/28/94	Tibor Sipos			
	5,260,074 ✓	11/09/93	Tibor Sipos			
	4,079,125 ✓	03/14/78	Tibor Sipos			
	4,280,971 ✓	07/28/81	Wischniewski			
	5,378,462 ✓	01/03/95	Boedecker et al.			
	6,313,296 ✓	11/06/01	Sham et al.			
	6,303,786 ✓	10/16/01	Deason et al.			
	6,284,767 ✓	09/04/01	Sham et al.			
	6,251,906 ✓	06/26/01	Chen et al.			
	6,184,241 ✓	02/06/01	Baures			
	6,180,634 ✓	01/30/01	Vacca et al.			
	6,147,095 ✓	11/14/00	Ferry et al.			
	6,117,999 ✓	09/12/00	Babu et al.			

FOREIGN PATENT DOCUMENTS

Document Number	Date	Country	Class	Subclass	Translation Yes No

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	Am. J. Gastroenterol (2001) 96:1831-1837
	Sherman et al., Clinical Infectious Diseases, (2000) 30:408-414
	Merck Index (2001) 13 th Edition; All antiviral
EXAMINER	DATE CONSIDERED
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	